Pleuropulmonary Amebiasis

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IT IS WELL DOCUMENTED that Entameba histolytica may secondarily involve the pleural and pulmonary tissues. This complication follows a primary invasion of the intestine by the parasite. While that sequence of events is readily appreciated by most clinicians, the fact that thoracic symptoms may be the sole signal of amebiasis does not always enter the mind of the examining physician.

The disastrous outcome of unrecognized and untreated pleuropulmonary amebiasis as opposed to the satisfactory, and often dramatic, response to antiamebic therapy serves to remind us that the problem is not one of treatment but of recognition. A glance at the *treatment* and *result* columns of Table 1 will further emphasize this point. Of the four patients who died, none received antiamebic therapy. The disease progressed without the diagnosis of pleuropulmonary amebiasis.

The present study was undertaken because of the experience gained in the diagnosis and management of ten cases observed between the years 1942 and 1955.

INCIDENCE

A recent study, in Oregon, by Rinehart and Marcus[20] placed the incidence of subclinical amebiasis at 30 per cent of the general population. The relationship between rheumatoid arthritis and amebiasis was discussed by Rinehart.[19]

Ochsner and DeBakey in a collected series of 2,490 cases of liver abscess found 209 (8.3 per cent) lung complications and 190 (7.5 per cent) pleural complications.[18] Thus, about a 15.8 per cent incidence of pleuropulmonary amebiasis following amebic hepatic abscess can be expected.

PATHOGENESIS AND PATHOLOGY

A brief review of the disease as a whole will be of aid to a better understanding of the thoracic complications. The parasite travels from person to person via fecal contamination of food and drink. Certain animals and insects are known to harbor Entameba histolytica. It has not been established just how important this latter reservoir of infection is for man.[3]

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• Pleuropulmonary amebiasis may be manifest without diarrhea or dysentery.

In obscure lesions of the right lower lung field, one should always consider pleuropulmonary amebiasis — especially with low grade fever and moderate leukocytosis.

Abscess and empyema contents should be examined promptly microscopically or kept warm to preserve the motility of the trophozoites until satisfactory examination is possible.

Conservative therapy will successfully manage most cases of pleuropulmonary amebiasis.

If a thorough search fails to reveal Entameba histolytica, and the diagnosis is still entertained, a medical therapeutic trial is in order.

The ingested cysts traverse the stomach and small intestine to the terminal ileum unchanged. At this point, the cyst wall becomes permeable and four nucleated motile ameba emerge.[3] According to Craig,[3] this excystation probably occurs in the region of the ileocecal valve. Some of the motile parasites invade the mucous membrane of the bowel and multiply in the tissues as trophozoites. Others which fail to invade the mucous membrane of the bowel multiply as trophozoites in the lumen for an undetermined period, then encyst. The parasites are finally voided in the feces as cysts or trophozoites. If the cysts reach another host, the cycle is repeated. Usually, the trophozoites journey from the intestine to the liver via the portal circulation. Here, amebic hepatitis occurs. If thrombosis and infarction result from the lytic activity of the parasites, an hepatic abscess occurs. Progression of this abscess may incorporate the diaphragm, so that the stage is set for pleuropulmonary complications by direct extension. After penetration of the diaphragm, three possible pathological situations may develop. These are empyema, lung abscess or bronchohepatic fistula.[18] Combinations of these lesions may occur (see Figure 1).

The parasites may reach the pulmonary parenchyma by the hematogenous route, as well as by direct spread. This, however, appears to be uncommon. It is generally agreed that there are three possible routes of spread by the blood stream. These are by the middle and inferior hemorrhoidal veins, the hepatic veins and by way of the intestinal lymphatic chain through the thoracic duct.[18] The resultant pathological states include either a solitary lung abscess or concomitant separate liver and lung abscesses (see Figure 2).

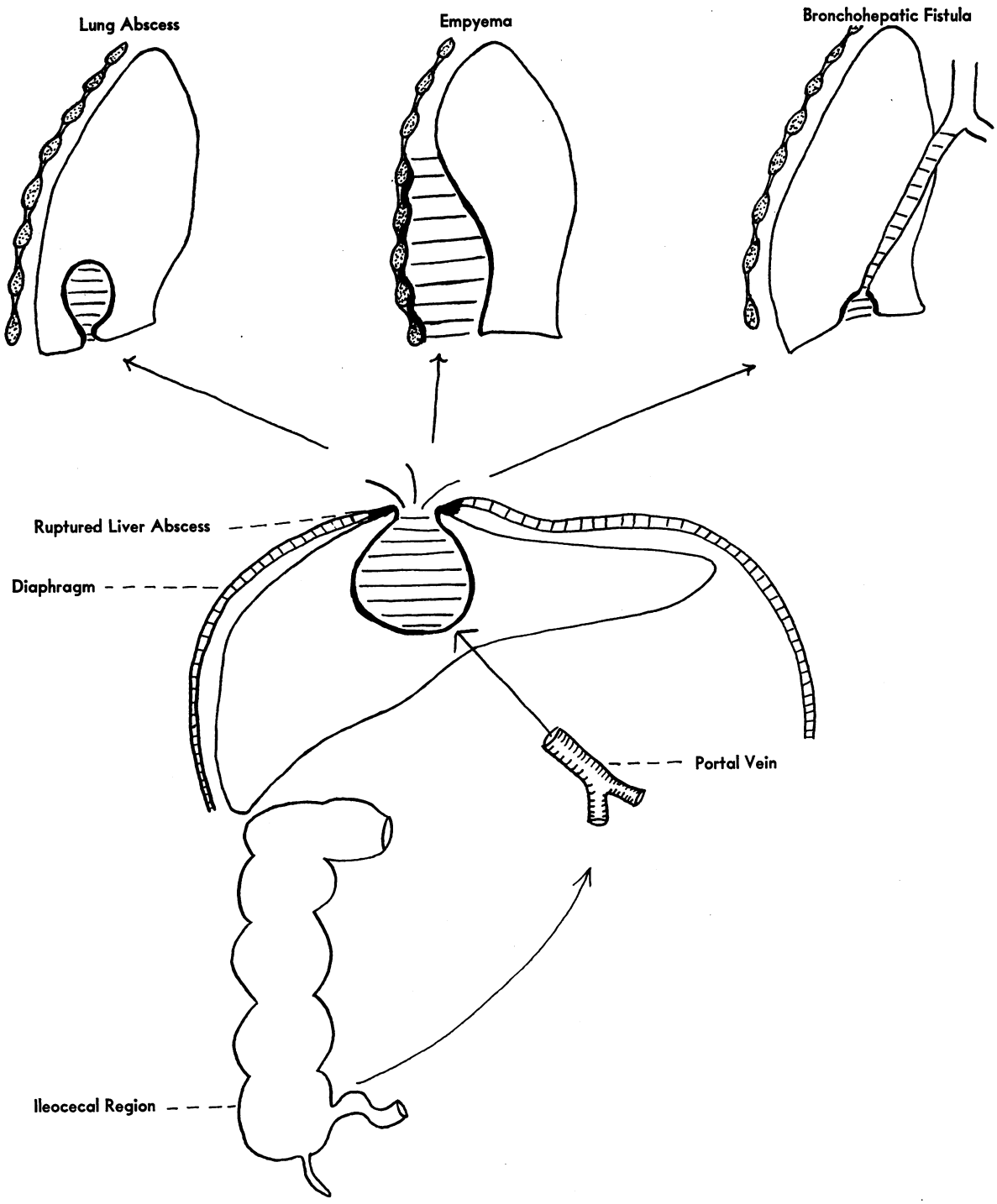

Figure 1.—Pathogenesis of pleuropulmonary amebiasis by direct extension from liver abscess (modified from Ochsner and DeBakey[18]).

Early experimental work (1914, 1928) indicated that the venous blood flow from the right side of the colon tended to pass to the right lobe of the liver, while blood flow from the left side tended to pass to the left lobe of the liver.[1,4] Recent experimentation casts doubt on this concept.[2] However, it may explain, in part, the fact that the common site for the formation of liver abscess is the right lobe of the liver. The inference being that the ileocecal lesion spreads by the portal blood stream to the right lobe of the liver and penetrates its convex surface to incorporate the diaphragm.

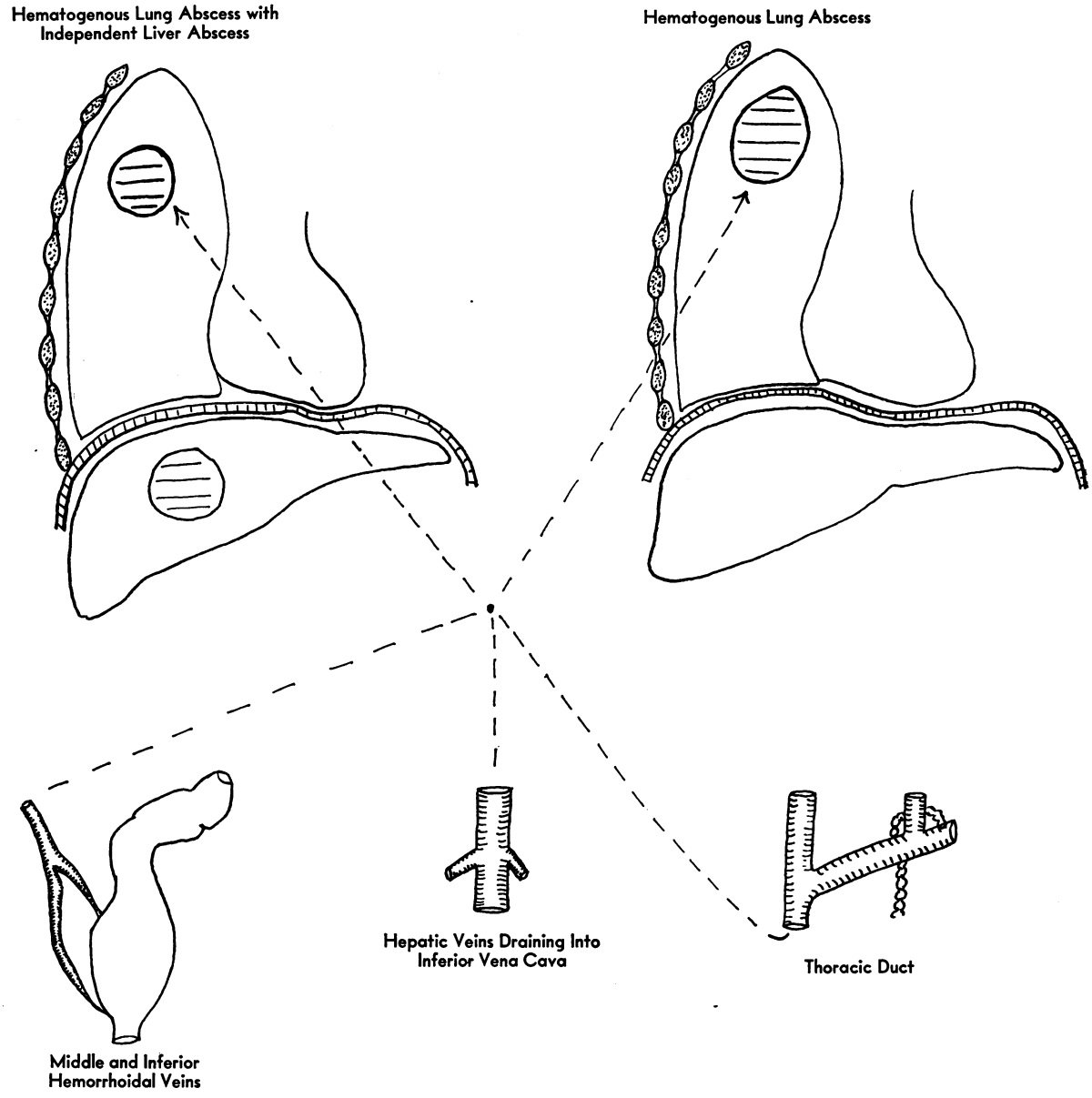

Figure 2.—Pathogenesis of hematogenous pleuropulmonary amebiasis by the three possible routes of spread (modified from Ochsner and DeBakey[18]).

Abscess formation in the left lobe of the liver is infrequent. Pericarditis as a sequela has been described.[17,21]

The contents of a hematogenous amebic pulmonary abscess are purulent, and are not considered characteristic.[18] The pulmonary amebic abscess formed by direct extension is considered characteristic. Its contents have been described as resembling "chocolate sauce" or "anchovy paste." Abscesses of this latter type do not contain purulent matter, but a mixture of blood, cytolyzed liver tissue and small solid particles of liver parenchyma which have resisted dissolution.[16] When a "chocolate sauce" abscess becomes secondarily infected, the contents change to a purulent character. This may be manifested by a greenish or grayish yellow creamy color.[16]

DIAGNOSIS

A strong index of suspicion should serve to keep physicians alerted for this condition. Lesions of the right lower lung, especially those of obscure etiologic lineage, should not be dismissed without a thorough search for Entameba histolytica.

Dysenteric symptoms have long been associated with amebiasis but they may be entirely absent or

TABLE 1.—*Analytic Data on Ten Cases of Pleuropulmonary Amebiasis.*

Case	Age	Sex	Leukocytes per cu. mm.	Initial Diagnosis	Diagnosis Confirmed by	Treatment	Lesions	Result
1.	43	M	12,700	Lung tumor	Pulmonary resection	Left upper lobectomy	Lung abscess	Died
2.	49	M	11,800	Pulmonary tuberculosis	Autopsy	No specific therapy	Lung abscess Liver abscess	Died
3.	35	M	11,500	Cholecystitis	Autopsy	Sulfathiazole	Bronchohepatic fistula Liver abscess Pleural effusion	Died
4.	54	M	10,900	Subphrenic abscess	Autopsy	Drainage attempted Antibiotics	Bronchohepatic fistula Lung abscess Liver abscess	Died
5.	38	M	19,800	Pneumonia	Pleural biopsy	Thoracostomy Emetine Carbarsone	Empyema Lung abscess Liver abscess	Recovered
6.	43	M	10,300	Pneumonia	Therapeutic response	Emetine Carbarsone	Lung abscess Liver abscess	Recovered
7.	39	M	7,800	Pulmonary tuberculosis	Stool studies Pneumoperitoneum	Emetine Chloroquine Carbarsone	Lung abscess Liver abscess	Recovered
8.	53	F	not determined	Amebiasis	Sputum studies	Emetine Carbarsone	Lung abscess Liver abscess	Recovered
9.	39	F	9,000	Pulmonary tuberculosis	Pleural exudate studies	Thoracostomy Emetine Chloroquine Carbarsone	Empyema Lung abscess Liver abscess	Recovered
10.	61	M	4,500	Pneumonia	Therapeutic response	Chloroquine Diodoquin® (diiodohydroxyquin)	Liver abscess Lung abscess	Recovered

dysentery may have occurred in the remote past so that the patient has forgotten about it. A 20-year or even as much as a 43-year interval may elapse between the dysenteric and the hepatitic stage.[6,17] In the case in the present series (Case 1, Table 1) 20 years elapsed between ulcerative proctitis and the onset of pulmonary symptoms. It is notable that in the list of symptoms (Table 2) in the present series, diarrhea and dysentery are absent.

Hepatic lesions, in the absence of dysentery, are more likely to occur in infection of the right side of the colon. In contrast, lesions of the left side of the colon are more likely to be associated with dysentery.[5,17]

Diaphragmatic involvement by the expanding liver abscess may produce pain in the right shoulder and discomfort low in the chest on the right side. Abdominal pain in the region of the right costal margin, due to an enlarging liver, may be mistaken for the pain of gallbladder disease. Often the liver is definitely palpable and tender.

A nonproductive cough due to irritation of the bronchi in the right lower lung may progress to a

TABLE 2.—*Symptoms Noted in Ten Cases of Pleuropulmonary Amebiasis.*

Symptom	No. Cases
Cough	10
Loss of weight	7
Excessive sputum	6
Thoracic pain	5
Hemoptysis	4
Dyspnea	2
Abdominal pain	1
Weakness	1
Fatigue	1
Tachypnea	1
Shoulder pain	1

TABLE 3.—*Physical Signs Observed in Ten Cases of Pleuropulmonary Amebiasis.*

Signs of	No. Cases
Fever	10
Consolidation, right lower lung	7
Enlarged tender liver	4
Emaciation	2
Consolidation, left upper lung	1
Pleural fluid	1

productive cough and the expectoration of "chocolate sauce."

Wasting, at times, is so pronounced that the situation may appear hopeless to a casual observer. This is especially true when the hepatic and pulmonary lesions remain undiagnosed for a considerable period.[10] The presence of cachexia, in company with a pulmonary lesion, should direct one's thoughts toward pulmonary amebiasis as well as pulmonary tuberculosis and carcinoma.

Upon physical examination of the chest, signs of pleural fluid or pulmonary consolidation or abscess may be noted. An enlarged tender liver with the above findings in the right hemithorax is very suggestive (see Table 3).

A hemogram, while not diagnostic, often supplies additional evidence for the recognition of the disease. Anemia may be present. Leukocytosis of a mild degree may be expected. It is quite probable that pronounced leukocytosis indicates secondary bacterial invasion of the amebic process. In general, there is moderate leukocytosis without much change in the proportion of polymorphonuclear leukocytes[17] (see Table 1).

Roentgenography offers considerable assistance. The main findings are localized to the right lower lung field and the right hemidiaphragm. Hematogenously induced pulmonary amebiasis is the exception (see Figure 3). The roentgenographic features will vary with the stage of advancement of the morbid process. The right hemidiaphragm may be elevated. Fluoroscopy may show the hemidiaphragm fixed. A localized superior bulge may indicate an underlying liver abscess which should be distinguished from a herniated liver.[9] Pneumoperitoneum[22] is of value to demonstrate a connection between the liver and hemidiaphragm (Figure 4). Actual invasion of the pulmonary parenchyma will be indicated by the visualization of a triangular infiltrate with the apex toward the hilum of the lung and the obliteration of the cardiophrenic angle (Figure 5) or an abscess cavity. The latter may or may not contain fluid, depending upon the presence or absence of a bronchial communication. If the pleural space were involved, the usual manifestations of pleural fluid would be present. Transient pulmonary infiltrations as noted in Loeffler's syndrome have been described in association with pulmonary amebiasis.[8] Pulmonary cavitation which persists after adequate antiamebic therapy probably is coincidental and not etiologically associated with Entameba histolytica.

Discovery of the cysts or trophozoites in the sputum, pleural exudate or stool establishes the diagnosis. Five stool examinations with intervals of several days should be the minimum.[13] If the pleural

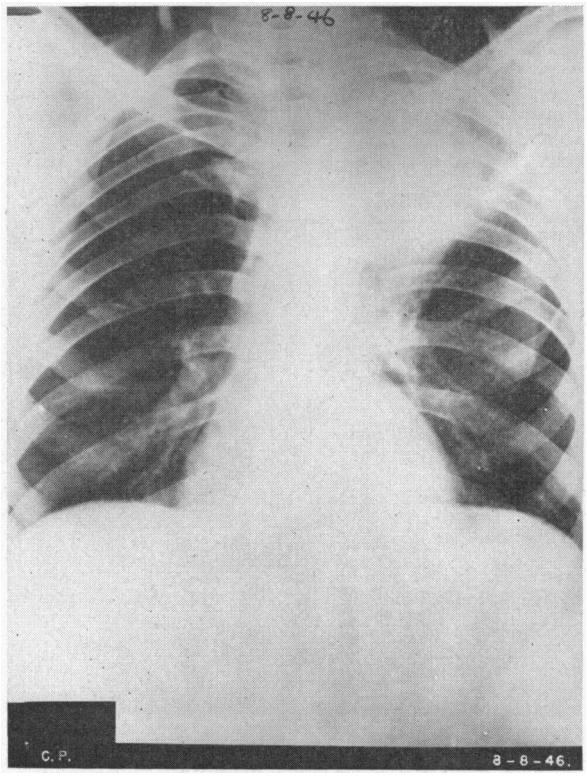

Figure 3 (Case 1).—Note the unusual position of the pulmonary amebic abscess in the left upper lobe. This represents the end result of hematogenous spread.

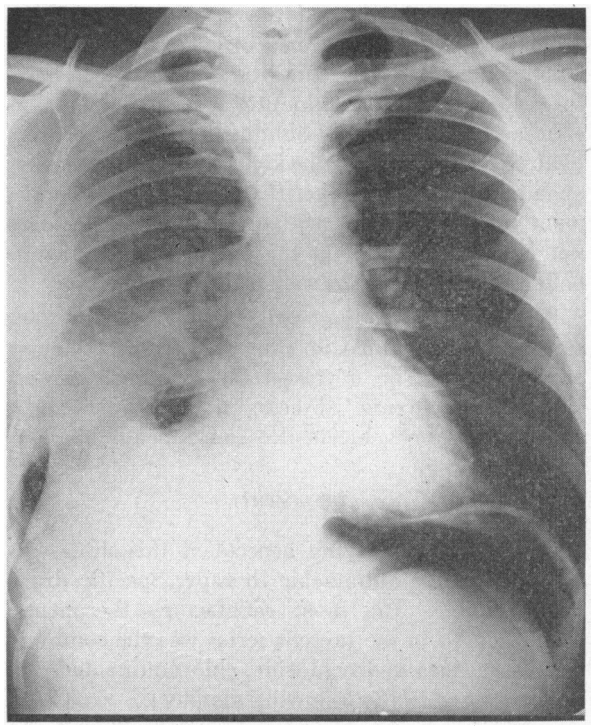

Figure 4 (Case 7).—Showing the value of pneumoperitoneum. A connection between the liver, diaphragm and lung may be readily demonstrated.

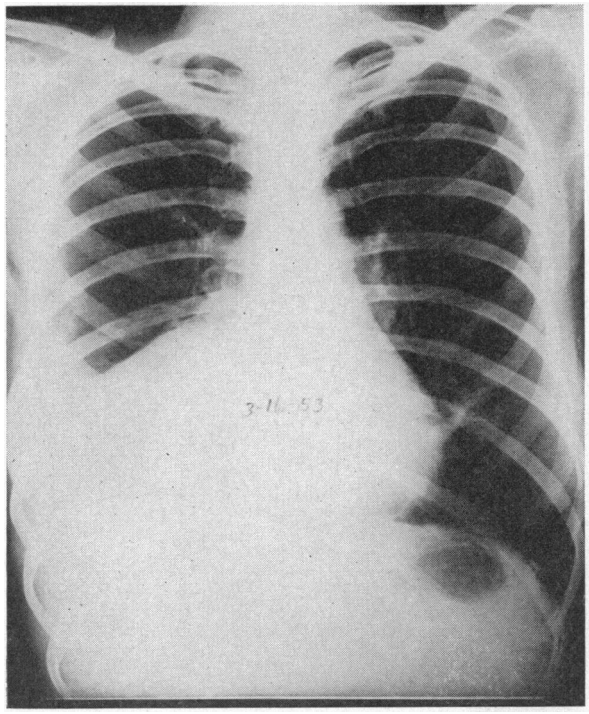

Figure 5 (Case 9).—Demonstrates the triangular infiltrate of the right lower lung field with obliteration of the cardiophrenic angle.

space is inadvertently drained, the diagnostic value of a pleural biopsy should not be overlooked. Collection and examination of the specimen should be done with care. It must be borne in mind that the trophozoites lose their motility as they cool. Therefore, microscopic examination should be done as soon as the specimen is obtained. If this is impractical, the specimen must be kept warm until adequate examination can be done. If the result of a complement fixation test is positive but trophozoites cannot be demonstrated in the stool, some clinicians believe extraintestinal amebiasis is indicated.[15,25]

The commonest diagnostic errors in the present series are exemplified in Table 3. Pleuropulmonary amebiasis may be mistaken for pulmonary tuberculosis, subphrenic abscess, tumor, pneumonia, cholecystitis, bronchiectasis[11] and appendicitis.[12]

TREATMENT

One of the gratifying aspects of this disease is the response to antiamebic therapy. Specific drugs are available. The most satisfactory therapeutic regimen used in the present series was the combination of emetine hydrochloride, chloroquine and carbarsone, used in the following manner:

a. Emetine hydrochloride subcutaneously, 1.0 mg. per kilogram of body weight daily, given 4 to 6 days, followed by,

b. Chloroquine orally, 0.5 gm. two times per day for 2 days, then 0.25 gm. two times per day for 14 to 20 days, followed by,

c. Carbarsone, 250 mg. two times per day for 10 days.[23]

Craig[3] noted that the effectiveness of emetine is limited mainly to the destruction of the trophozoite form. Further, he noted that with blood content at therapeutic levels the cystic forms are not inactivated. Chloroquine has its greatest activity in amebiasis of the extracolonic type. Thus, while emetine hydrochloride and chloroquine are appropriate for pleuropulmonary and hepatic amebiasis,[24] they are not the drugs of choice for intestinal amebiasis. The latter condition should be treated with one of the iodine or arsenical amebicides to rid the intestinal tract of Entameba histolytica. Chlorotetracycline (aureomycin) has been used effectively in pleuropulmonary amebiasis.[7] It may be useful if emetine is not tolerated. Since the advent of so effective a therapeutic agent as chloroquine, the value of emetine hydrochloride has decreased. It may be that the indications for emetine will narrow to the occasional case in which there is need for parenteral use.[14]

Aspiration of amebic liver abscess has been recommended.[17] However, what with the potent antiamebic drugs now available, aspiration is probably rarely indicated.

Unquestionably, pulmonary resection will be done in some cases of pulmonary amebiasis in which abscess or infiltrate is manifest but in which the diagnosis is undetermined preoperatively. While pulmonary resection is not indicated, pleuropulmonary amebiasis can be handled satisfactorily after such a procedure providing it is recognized and antiamebic therapy instituted early.[7,10] In general, the authors are of the opinion that operation should be avoided if possible.

The diagnosis is often difficult to confirm.[26] If pleuropulmonary amebiasis is suspected, a therapeutic trial with drugs is in order. It may establish the diagnosis as it resolves the treatment problem.

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Carbutamide Clinical Trial Suspended

ELI LILLY AND COMPANY has announced the suspension of the fifteen-month clinical trial of carbutamide, or BZ-55. Carbutamide is a sulfonamide derivative which controls many cases of diabetes when given by mouth.

In a statement, Dr. Kenneth G. Kohlstaedt, director of the clinical research division, said in part:

"We have communicated this decision to some 2,900 physicians who have been testing carbutamide in more than 10,000 patients. Discontinuing use of the drug involves no danger to the patients who have been controlling their diabetes with it. They may safely return to their former method of control.

"We are not unmindful of the fact that 40,000 patients in Germany have taken carbutamide without any serious side effects being reported by German investigators. Nor are we unmindful of the fact that in our own studies 95 per cent of those patients who are able to control their diabetes with carbutamide appear to be able to do so for months without untoward effects. However, among the other 5 per cent there have been a few serious side reactions to the drug which are identical to those experienced with other sulfa drugs.

"In view of these findings, and in full consideration that carbutamide is a drug of convenience rather than necessity, Eli Lilly and Company believes it is prudent to suspend the clinical trial pending further investigation."